REMARKS

In an Office Action dated March 13, 2009, the Examiner incorrectly stated the status of the claims; Claims 1 and 3-21 are pending, Claim 2 is cancelled, Claims 5, 6, 11, and 14-16 are withdrawn, and Claims 1 and 3, 4, 7-10, 12, 13, and 17-21 are under consideration. The Examiner withdrew the rejections of record in view of Applicants' response, but imposed new rejections allegedly necessitated by Applicants' amendments. Applicants note that the status of Claim 21 is uncertain since the Examiner failed to include this claim in the claim status statement and neither rejected nor allowed it. In light of the amendments above and for the reasons noted below, Applicants respectfully request reconsideration.

A Request for Examination accompanies this response.

Claim Amendment

Applicants amend Claims 1, 7, and 17 to recite that the genetic construct is introduced by electroporation into clumps of human ES cells. Support for the amendment is provided by paragraphs [00026], [00030] and [00045]. Applicants further amend Claims 1, 7, and 17 to clarify that the 5' and 3' arms portions of the vector are homologous to regions flanking the site selected for insertion so that homologous recombination can occur. Support for the amendment is provided by paragraph [00020] of the specification. It is well-known in the art, and explained in the specification, that the arms are homologous to regions flanking the site selected for insertion. The amendment avoids ambiguous claim language that might have been erroneously read to mean that the insert is homologous to the regions flanking the site selected for insertion.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 1, 4, 7, 8, 10, 12, 17, and 18-20 for alleged obviousness over Smith *et al.*, in view of either Jaynes *et al.* or Chalitta-Eid (as evidenced by Tenner *et al.*) or Pinson *et al.* The Examiner further rejected Claims 3, 9, and 13 for alleged obviousness over Smith *et al.*, in view of either Jaynes *et al.* or Chalitta-Eid (as evidenced by Tenner *et al.*), in further view of West *et al.*

Smith does not make obvious the amended claims because Smith, alone or in combination with any of the cited documents, does not teach or suggest electroporation of clumps of human ES cells. Smith discloses electroporation of murine ES cells in phosphate buffered saline (col. 7, line 19-38). Even if Smith suggested electroporating clumps of murine

ES cells in medium, which it does not, Smith cannot constitute an enabling disclosure of homologous recombination into human pluripotent stem cells because neither the properties nor the culturing conditions of such human cells were known as of Smith's filing. Smith's filing date predates the public disclosure of human embryonic stem cells. Even if human embryonic stem cells had been known at Smith's filing, the intervening public knowledge of human embryonic stem cell culture cannot simply be combined with the Smith disclosure because the methods then known for targeting homologous recombination by electroporation were non-enabling in human embryonic stem cells, as Applicants and the Examiner have noted throughout prosecution of this application.

Neither Jaynes, Chalitta-Eid, Tenner, nor Pinson can compensate for Smith's shortcomings. Jaynes discloses that applying an electric field renders cells more porous to entry of foreign DNA fragments in the medium (Jaynes, col. 7, lines 1-7). Chalitta-Eid shows that a vector can be introduced into an embryonic stem cell line by electroporation and can undergo homologous recombination with the cell's DNA (Chalitta-Eid, col. 35, lines 16-19). Tenner teaches replating ES cells in medium subsequent to electroporation. Pinson teaches electroporating murine ES cells using a GenePulser at 320 Volts and 250 micro Farads (Pinson, page 118, left column, "transfection and screening of ES cells") but does not teach using only a single pulse, as the Examiner alleged. Importantly, no document teaches or suggests electroporation of DNA into clumps of human ES cells.

The Examiner rejected Claims 3, 9, and 13 for alleged obviousness over a combination of Smith and Jaynes or Chalitta-Eid, discussed above, with West *et al.* West cannot overcome the shortcomings of Smith, Jaynes, and Chalitta-Eid. West merely teaches inserting DNA markers into human genes by homologous recombination of promoterless constructs. Neither Smith, nor Jaynes, nor Chalitta-Eid, nor West disclose, teach, or suggest performing the electroporation method on clumps of ES cells.

Applicants note the Examiner's flawed understanding of the state of the art as of the filing date. The Examiner alleged that "electroporation of hES cells was not known to be highly successful at the time of filing" (Office Action, page 8, third paragraph). This understates the inventors' achievement. Indeed, electroporation was known to not work in a useful manner (see Benvenisty; see also specification, [00026]) and the inventors were the first to successfully

introduce targeted modifications into human ES cells by devising suitable methods including the conditions recited in the claims.

For the reasons stated herein, this application is now believed to be in condition for allowance and such action is respectfully requested. Applicants respectfully ask the Examiner to contact Applicants' attorney directly to expeditiously resolve any remaining issues.

Fees

A Petition for an extension of time for one month accompanies this response so the response will be deemed to have been timely filed. Please charge the Petition fee and the fee for the Request for Continued Examination to Deposit Account No. 17-0055. If any other extension is due in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee due to the same Deposit Account. No other fee is believed due, but if any other fee is due in this or any subsequent response, please consider this to be a request to charge the fee to the same Deposit Account.

Respectfully submitted,

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